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SUPPLEMENT ARTICLE

Contact With Young Children Increases the Risk of Respiratory Infection in Older Adults in Europe—the RESCEU Study

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Background. Knowledge about how older adults get a respiratory infection is crucial for planning preventive strategies. We aimed to determine how contact with young children living outside of the household affects the risk of acute respiratory tract infections (ARTI) in community-dwelling older adults.

Methods. This study is part of the European RESCEU older adult study. Weekly surveillance was performed to detect ARTI throughout 2 winter seasons (2017-2018, 2018-2019). Child exposure, defined as having regular contact with children under 5 living outside of the subject's household, was assessed at baseline. The average attributable fraction was calculated to determine the fraction of ARTI explained by exposure to these children.

Results. We prospectively established that 597/1006 (59%) participants experienced at least 1 ARTI. Child exposure increased the risk of all-cause ARTI (adjusted odds ratio [aOR], 1.58; 95% confidence interval [CI], 1.21 -2.08; $P = .001$). This risk was highest in those with the most frequent contact (aOR, 1.80; 95% CI, 1.23-2.63; $P = .003$). The average attributable fraction of child exposure explaining ARTI was 10% (95% CI, 5%-15%).

Conclusions. One of 10 ARTI in community-dwelling older adults is attributable to exposure to preschool children living outside of the household.

Clinical Trials Registration. NCT03621930.

Keywords. respiratory infection; elderly; child exposure; community.

Respiratory tract infections (RTI) are the leading cause of disease worldwide with an estimated annual incidence of 17.2 billion upper RTI, and 291 million lower RTI [1]. Most respiratory infections are of viral etiology. Common respiratory viruses in both children and adults are influenza virus, respiratory syncytial virus (RSV), rhinovirus, coronaviruses, parainfluenza viruses, metapneumovirus, adenoviruses, and bocaviruses [2]. The incidence of respiratory infections is highest in childhood and decreases with older age [3]. However, most severe disease occurs in the extremes of the age spectrum [4]. This is illustrated by the fact that 45% of all worldwide deaths due to lower RTI occur in adults older than 70 years [4]. It is therefore important to protect this vulnerable older age group and decrease their risk of getting infected. We are aware that young children are a reservoir of (viral) respiratory pathogens and their role in introducing RTI into their households has been well established [5–7]. Contact with children increased the risk of RTI in the adult population in other studies [8–10]. But despite many transmission studies in various settings [5–7, 11–20], the role of young children in the occurrence of RTI in older adults that live outside of the child's household is not well known. Because the majority of older adults live independently of children in Europe and North America [21], understanding the source of infection and the transmission patterns in this setting is fundamental to determine how preventive strategies should be deployed. The pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) underlines once more the necessity of having a thorough understanding of how social contacts drive the risk of RTI in this vulnerable population to determine the impact of preventive strategies such as which isolation measures should be taken. The Respiratory Syncytial Virus Consortium Europe (RESCEU) study was performed during 2

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winter seasons to investigate the burden of disease of RSV in community-dwelling older adults [21]. In this current study, we aimed to investigate the contribution of child exposure to RTI in community-dwelling older adults from the RESCEU study.

METHODS

Participants of the prospective RESCEU older adult cohort study were analyzed. The study design and data collection have been described previously [22]. In summary, the RESCEU older adult study is a European multicenter, prospective, observational cohort study conducted across 2 consecutive RSV seasons (2017–2018 and 2018–2019) in the Netherlands, Belgium, and the United Kingdom. In each season a cohort of community-dwelling adults of at least 60 years of age was recruited from 17 general practitioners' offices before the start of the RSV season (defined as 1 October to 1 May), and followed up during 1 RSV season. General practitioners' offices were located in urban and suburban areas. More detailed information about the RESCEU older adult study can be found at Clinicaltrials.gov, identifier: NCT03621930.

The study was approved by the Ethical Review Authority in Belgium (reference No. B300201732907), the Netherlands (reference No, NL60910.041.17), and United Kingdom (ethics reference 17/LO/1210, Integrated Research Approval System [IRAS] reference 224156). Participants gave informed consent before taking part in this study. The study was conducted according with the Declaration of Helsinki, as revised in 2013.

Respiratory Infections

Between 1 October and 1 May during the seasons 2017-2018 and 2018-2019, the participants were contacted weekly by email or telephone by the study team to ask for presence of respiratory symptoms. We defined an acute respiratory tract infection (ARTI) as the presence of 1 or more of the following symptoms for at least 1 day: nasal congestion or discharge, cough, wheezing, or shortness of breath. When a participant fulfilled this ARTI case definition, a home visit was scheduled within 72 hours. During the home visit 2 nasopharyngeal swabs were collected for viral diagnostics (FLOQSwab, 3 mL UTM Xpert viral transport medium, Copan diagnostics, and MicroTest M4RT, Remel). RSV and influenza were tested within 24 hours after collection using a point-of-care qualitative polymerase chain reaction (PCR; Xpert Xpress Flu/RSV assay, Cepheid, Sunnyvale, CA, USA [23]. RSV was also validated in the second nasopharyngeal sample using quantitative PCR after the study. Because this study was performed as part of an RSV burden of disease project, we did not evaluate other viruses or bacterial causative agents in this study. We therefore stratified for all-cause ARTI, RSV-ARTI, and influenza-ARTI. New episodes of ARTI were defined as either ARTI symptoms after a symptom-free interval of at least 1 week following a previous ARTI episode or a sudden increase in symptom severity of an existing ARTI, including development of new symptoms.

Exposure

Several exposure variables were measured by questionnaire during a baseline home visit before the start of the RSV season (August/September). This included if participants generally had close contact with children younger than 5 years that were living outside of the subject's household and, if so, how often they would see these children. It was indicated in the questionnaire that the contact had to be substantial, for example contact with a visiting grandchild. Exposure to children was stratified as having frequent (weekly), infrequent (less than weekly), or no contact, irrespective of the number of children they had close contact with. Additionally, the number of human contacts during the past 24 hours as a proxy of average daily contacts, employment status, and household composition were recorded. We defined households as those living alone and those living with a partner. Participants that lived together with children were excluded from the analysis. We calculated ARTI attack rates in those living alone and those living with a partner using a subcohort of participants that lived together and both participated in the study. The secondary attack rate, that is the rate of those infected by an infected household partner, was calculated in this subcohort. Details of the estimation of the attack rates are provided in the Supplementary Material.

Statistical Analysis

Univariate logistic regression was used to approximate the risk of all-cause ARTI for individual risk factors. Subsequently, all exposure variables with a univariate P value < .10 were included in a multivariable logistic regression model that was adjusted for confounders. Potential confounders for the association between exposure variables and ARTI were based on literature and selected based on the highest correlations with the aforementioned exposure variables observed in a correlation matrix. No variable selection was performed and adjusted estimates were obtained from the full model. Similarly, models were developed for RSV-ARTI and influenza-ARTI, although these were considered explorative because of limited power due to the low number of cases. In these explorative models, single univariate predictors ($P < .10$) were included in the multivariable model together with a fixed set of confounders, including age, frailty score, and comorbidity.

We estimated the contribution of child exposure to the occurrence of ARTI by calculating the population-attributable risk and average attributable fraction. Both metrics combine the effect size of a risk factor with its prevalence in the studied population to provide an estimate of the fraction of disease that could be explained by that risk factor. The population-attributable risk was calculated using the unadjusted relative risk (RR) and the prevalence of exposure among cases (P_e) using the formula: $P_e\ (RR - 1)/\ 1 + P_e\ (RR - 1)$. We thereafter calculated the average attributable fraction, which was corrected for other exposure variables and confounders [24]. The

average attributable fraction is calculated by modelling disease occurrence as a function of predictors (of which child exposure was of interest). By removing variables from the model one can estimate the variables' contribution to the disease occurrence. Averaging all attributable fractions from every possible permutation for which different predictors could be excluded from the model provides the average attributable fraction per included predictor. Details of the average attributable fraction can be found in the Supplementary Material. No imputation of missing data was performed and all analyses were performed in R version 4.0.1. The Averisk package was used for calculating the average attributable risk [24].

RESULTS

In total, 1040 participants were included in the RESCEU study, of whom 1006 (97%) lived in a household without young children. At least 1 ARTI was experienced by 597/1006 (59%) participants during the course of the study (range, 1–5). Eight patients (0.9% of ARTI) were hospitalized while 211 had an outpatient visit (26% of ARTI). In total, 822 ARTIs were reported in these 597 patients, of which 783 ARTIs were visited by the study team for diagnostic testing at the moment of infection. RSV was detected by PCR in 35/783 (4.5%) ARTI episodes in 35 individual patients while 58/783 (7.4%) ARTI episodes were positive for influenza by PCR in 57 individual patients (1 patient had 2 separate influenza infections). No RSV-influenza coinfections occurred. Most respiratory infections were PCR negative for RSV and influenza (termed other ARTI). The characteristics of study participants are displayed in Table 1. The subcohort of participants that lived with their partner and participated together in the study included 316 individuals (158 households). In total, 39 missed visits in 39 patients were registered (ie, an infection was reported but no visit was performed). Missed study visits most often occurred because the infection

Table 1. Characteristics of Study Participants With and Without a Respiratory Infection

	No ARTI	ARTI		
Demographics	n = 409	All-Cause n = 597 [a]	RSV n = 35	Influenza n = 57
Age, y, median (IQR)	76 (70–81)	75 (68–80)	75 (70–80)	71 (67–78)
Female sex	212 (52)	322 (54)	20 (57)	29 (51)
Comorbidity, any	269 (66)	411 (69)	22 (63)	37 (65)
Cardiovascular	86 (21)	123 (21)	7 (20)	10 (18)
Pulmonary	38 (9)	78 (13)	5 (14)	7 (12)
Diabetes	18 (4)	60 (10)	2 (6)	5 (9)
Frail[c,b]	59 (16)	83 (15)	2 (6)	6 (11)
Influenza vaccination[d]	274 (72)	458 (80)	29 (85)	45 (79)
Pneumococcal vaccination[e]	41 (11)	72 (14)	4 (12)	10 (21)
Smoking	39 (10)	40 (7)	3 (9)	3 (5)
Household smoke exposure	50 (12)	62 (11)	3 (9)	5 (9)
Allergic, any[f]	97 (24)	168 (29)	9 (26)	15 (27)
Hay fever	22 (6)	32 (6)	3 (9)	2 (4)
House-dust mite	8 (2)	23 (4)	0 (0)	4 (7)
Exposure				
Exposure to children aged < 5 y[g]				
Any	174 (43)	328 (55)	18 (51)	33 (60)
Infrequent, less than weekly	113 (28)	197 (33)	7 (20)	22 (40)
Frequent, weekly	61 (15)	131 (22)	11 (31)	11 (20)
Household composition				
Living alone	140 (34)	198 (32)	6 (17)	18 (32)
Living with partner	267 (65)	395 (64)	28 (80)	39 (68)
Other, adults only	2 (1)	4 (1)	1 (2)	0 (0)
Daily contacts, median (IQR)	5 (3–10)	5 (2–10)	5 (4–9)	6 (3–15)
Employed[h]	49 (13)	71 (12)	6 (18)	8 (15)

Values are numbers and percentage of cases unless otherwise indicated. Missing data <1% is not shown, if more than 1% is missing, the percentages are added as footnote.

Abbreviations: ARTI, acute respiratory tract infection; IQR, interquartile range.

[a]Including the 35 RSV and 57 influenza patients.

[b]Scored using the Groningen Frailty Indicator questionnaire, a 15-item validated screening instrument to determine the level of frailty in adults, the cut-off for frail is at 4 points [25].

[c]Missing n = 74 (7%).

[d]Missing n = 52 (5%).

[e]Missing n = 89 (9%).

[f]Missing n = 19 (2%).

[g]Missing n = 11 (1%).

[h]Missing n = 38 (4%).

Table 2. Regression Analysis of Exposure Variables

	All-Cause ARTI (n = 597)		RSV (n = 35)		Influenza (n = 57)	
Risk Factor	Crude OR (95% CI)	aOR (95% CI)	Crude OR (95% CI)	aOR (95% CI)	Crude OR (95% CI)	aOR (95% CI)
Child exposure, any	**1.64 (1.27–2.11)*****	**1.58 (1.21–2.08)****	1.05 (.53–2.07)	…	1.51 (.87–2.67)	…
Child exposure infrequent, < weekly[a]	**1.51 (1.13–2.02)***	**1.48 (1.09–2.01)***	0.65 (.27–1.59)	…	1.65 (.90–3.04)	…
Child exposure frequent, weekly[a]	**1.86 (1.31–2.65)****	**1.80 (1.23–2.63)****	1.69 (.78–3.69)	…	1.30 (.62–2.73)	…
Living with partner[b]	0.99 (.76–1.29)	…	**2.31 (1.05–5.79)****	2.15 (.90–5.17) ±	1.13 (.65–2.03)	…
Infected partner	NA[c]	…	**5.18 (1.08–19.0)****	**4.81 (1.18–19.6)****	3.33 (.72–11.54)±	2.57 (.65–10.2)
Employed	0.97 (.66–1.43)	…	1.57 (.58–3.65)	…	1.09 (.47–2.23)	…
Number of daily contacts	1.00 (.99–1.01)	…	1.01 (.98–1.02)	…	1.01 (.99–1.02)	…

Abbreviations: ARTI, acute respiratory tract infection; CI, confidence interval; crude OR, univariate regression analysis odds ratio; aOR, adjusted odds ratio corrected for age, Groningen Frailty Indicator score, and comorbidity only in those with a univariate association $P < .10$.

±$P < .10$, *$P < .05$, **$P < .01$, ***$P < .001$. Significant values $P < .05$ are shown in bold.

[a]Compared to never.

[b]Compared to those living alone.

[c]Not determined because patients with multiple infections could not be classified for a single disease and exposure status in this analysis (ie, 1 participant could have been an index case while also been exposed to an infected partner during a separate infection).

was only mentioned after it was resolved or because participants were abroad. Characteristics of the total study population and the household subcohort are displayed in Supplementary Table 1.

Child Exposure

Any exposure to children younger than 5 years living outside of the household was reported in 51% (502/1006) of participants. Patients with influenza infection most often reported having contact with children (60%, 33/57), while those without any respiratory infection reported the least contact with young children (43%, 174/409). Frequent child exposure (weekly) was most often seen in RSV-positive patients (31%, 11/35) and was again lowest in those without ARTI (15%, 61/409; Table 1).

Child Exposure and ARTI

Child exposure was an independent risk factor for all-cause ARTI in multivariable regression analysis adjusted for age, frailty score, and comorbidity, which showed an adjusted odds ratio (aOR) of 1.58 (95% confidence interval [CI], 1.21–2.08; $P = .001$). A dose-dependent effect towards a higher risk was observed in those with more frequent contact (Table 2). Exposure to young children did not significantly affect the risk for RSV or influenza infection. The average attributable fraction adjusted for confounding and other exposure variables indicated that child exposure explained 10% (95% CI, 5%–15%) of all ARTI (Table 3). None of the other variables included in the model were statistically significant based on the confidence intervals.

Other Exposure

None of the exposure variables other than child contact were significant for ARTI. For RSV-ARTI the risk was significantly higher in those with a partner that was infected with RSV (aOR, 4.81; 95% CI, 1.18–19.6; Table 2). The secondary attack rate for RSV was also significantly higher compared to the population risk (21.3% vs 3.6%; Table 4). A similar trend was seen for influenza (18.8% vs 5.9%, $P = .18$).

Table 3. Average Attributable Fractions Explaining ARTI Occurrence

Variables	RR	Prevalence Among ARTI, %	PAR, %[a]	Average Attributable Fraction, % (95% CI)[b]
Child exposure, yes/no	1.24	55	10.5	10.0 (5–15)
Employed	1.00	13	0	0 (–3 to 2)
Living with a partner	1.05	65	2.8	0.5 (–7 to 8)
Number of contacts[c]	0.97	76	–2.2	–3.7 (–14 to 7)
Age >75 y	0.90	53	–5.7	–4.5 (–11 to 2)
Comorbidity	1.03	70	2.3	5.4 (–3 to 13)
Frail	0.95	15	–0.7	–0.6 (–3 to 2)
Female sex	1.03	54	1.4	1.6 (–5 to 8)
High educational level	1.06	42	2.3	2.1 (–3 to 7)

Abbreviations: ARTI, acute respiratory tract infection; CI, confidence interval; PAR, population attributable risk; RR, relative risk.

[a]Calculated as: $P_e (RR - 1)/ 1 + P_e (RR - 1)$ in which P_e is the prevalence of exposure among cases. The PAR is based on a crude relative risk and is therefore not corrected for correlations or confounding.

[b]Calculated with Averisk package, all variables in the table were included in the model to correct for confounding and correlations.

[c]Dichotomized as >2 contacts per day from number of daily contacts.

Table 4. Attack Rates of ARTI

Population	Cases	Denominator[a]	Attack Rate, %	95% CI
ARTI, at least 1				
Total study population	597	1006	59.3	56.3–62.3
In those living alone	198	338	58.6	53.3–63.7
In those living with partner[b]	189	316	59.8	54.3–65.1
Secondary cases, SAR	40	155	25.8	19.6–33.2
RSV-ARTI				
Total study population	35	968	3.6	2.6–5.0
In those living alone	6	322	1.9	.9–4.0
In those living with partner[b]	18	292	6.2	3.9–9.5
Secondary cases, SAR	3	14	21.4	7.6–47.6
Influenza-ARTI				
Total study population	57	967	5.9	4.6–7.6
In those living alone	18	322	5.6	3.6–8.7
In those living with partner[b]	21	288	7.3	4.8–10.9
Secondary cases, SAR	3	16[c]	18.8	7.5–43.0

Abbreviations: ARTI, acute respiratory tract infection; CI, confidence interval; SAR, secondary attack rate, the proportion of secondary cases occurring while the index case still experienced symptoms or within 7 days after the primary case is recovered, divided by the total number of exposed household contacts.

[a]Denominators for specific ARTI vary because of excluded missing visits.

[b]Participants from the household cohort are used for these estimations.

[c]Two patients had onset of influenza on the same date and were considered a coprimary case therefore 16/18 index cases exposed their partner to influenza.

DISCUSSION

We investigated how contact with young children living outside of the household affected the risk of ARTI in older adults living in the community. We showed that contact with young children increased the risk of all-cause ARTI in a dose-dependent manner and that child exposure explained 10% of all ARTI in the community-dwelling older adult population.

No studies to date have determined the direct transmission dynamics between young children and older adults living outside of the child's household. The role of young children in adult RTI has been pointed out for community-acquired pneumonia in adults and RSV in patients with chronic obstructive pulmonary disease [8, 26–28]. In another study, transmission of respiratory disease and carriage of *Streptococcus pneumoniae* was highest when interpersonal contact was physical and extended [29]. Additionally, they showed that contact from and with children aged <10 years involved proportionally more physical contact than contacts between older children and adults [29]. Importantly, this effect was not observed for short (less than 5 minutes), casual contacts. We hypothesize that transmission is likely to occur when grandparents babysit their grandchildren because contact is both extended and will involve physical contact. Patients with RSV infection in our study reported the highest proportion of frequent child exposure. Although we suspect an association between child exposure and RSV infection, we could not confirm this in our study because it was underpowered to show virus-specific associations.

Another clue towards the pivotal role of children in the spread of respiratory disease in the population comes from the experience with mass vaccination of school-aged children for influenza [9, 30–33]. The Japanese program that spanned over 3 decades resulted in a significant decrease of excess mortality from pneumonia, influenza, and all-cause mortality in all age groups [9]. More recent experiences from introduction of pediatric influenza vaccination in the United Kingdom indicated similar population benefits while also being cost-efficient [30–32]. They concluded that the most efficient way of reducing overall influenza-attributable morbidity and mortality appears to be to target the key spreaders, that is the children [30]. The best evidence comes from a randomized trial in which children aged 36 months to 15 years in Hutterite colonies in North America were cluster-randomized to receive either influenza immunization or hepatitis A vaccination [33]. A significant protective effect of influenza vaccination was observed for all community members in the intervention group [33].

The major strength of our study is the prospective follow-up in a large cohort of community-dwelling older adults. Participants were recruited before onset of ARTI in contrast to studies that use a case-ascertained design in which participants are only recruited upon medical attendance. Cases in these studies are likely to have been biased towards individuals with more severe symptoms that required a doctor's visit. More severe disease may affect the generalizability of risk factor analysis. Additionally, by calculating the average attributable fraction we were not only able to determine the effect size of child exposure on the individual level, but also showed how much of the ARTI risk could be attributed to this risk factor. Lastly, coparticipation of 316 older adult life partners in 158 households provided a unique opportunity to analyze infection rates in small households with only older adults.

There are also limitations to our study. First, exposure was assessed at baseline and was not verified at the moment of acute infection. While we quantified the average frequency of contact with young children, we did not prospectively log these contacts nor did we specify them for duration and setting. Also, the average contacts per day were based on 1 previous day and could therefore be imprecise. The next steps in understanding the role of infants as a source of infection in older adults are transmission studies performed upon contact at the homes of older adults. Second, we assume that the underlying mechanism of the association is based on viral transmission from children to older adults. Because not all RTIs have a viral etiology [34], we may have underestimated the effect size. We could only differentiate for RSV and influenza but were underpowered to robustly study these 2 specific viral pathogens. We expect transmission of RSV and influenza from young infants to older adults because these pathogens are prevalent in childhood. Third, our results may not be generalizable to those that live in nursing homes because we studied community-dwelling older adults and contact patterns might differ. Last, a large part of disease occurrence was not explained, warranting further research into the risk of infection from of contact with other age groups and other risk factors.

These findings are important for planning preventive strategies in the elderly population. Restricting contact with young children may be used to decrease the burden of RTI in the elderly population. While application of this restrictive measure might be feasible in times of epidemics or in very frail patients, there are obvious social and economic issues involved with sustaining these measures on a regular basis. Pediatric vaccination for respiratory pathogens may indirectly diminish the RTI burden in older adults, as discussed for influenza. Regional variance in household compositions (eg, children and older adults living together) can affect effectivity and feasibility of preventive measures [21]. Pediatric vaccination may be more beneficial in regions where children and elderly people more often share households. These types of shared households will conversely make social distancing strategies more difficult to achieve. A thorough understanding of social dynamics and regional differences is therefore crucial to tailor protective strategies.

CONCLUSION

We show that the risk of ARTI in older adults living in the community is increased because of contact with young children that do not live in the same household. More frequent contact was associated with a higher risk of ARTI and 10% of all ARTI could be attributed to contact with young children.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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